REMARKS

Claims 1-55 were pending. Claims 1-26 and 48-55 are canceled. Claim 27 has been amended. No new matter is added. Applicants respectfully request reconsideration of the rejections.

Applicants wish to thanks Examiners Calamita and Fredman for the telephone interview of February 16, 2005. As discussed in the interview, a Declaration under 37 C.F.R. 1.132 is provided herewith.

Support for the amending language "mismatch corepair event" may be found throughout the specification. For example, in the summary of the invention (page 5, lines 17-21) it is stated "The method comprises detecting, for any of the plurality of duplexes, an alteration in a characteristic of a cell, where the alteration in cellular phenotype is caused by corepair of a marker that is present together with the duplex in a vector within the cell, wherein the corepair is initiated by a mismatch that is present in the duplex." (underlining added)

MRD reports a mismatch in a DNA "test" duplex by its ability, when included within a replicable vector, to initiate *in vivo* corepair of a phenotypically sortable genetic element ("marker") present elsewhere in the vector as an otherwise "uncorrectable" heteroduplex. By "phenotypically sortable" is intended a genetic element that confers upon the cell a distinguishable phenotype. Because repair of the marker mismatches is directional - that is, reproducibly in favor of the sequence of one of the two strands of the marker heteroduplex - the two strands of the marker heteroduplex can be designed so that repair confers upon the host cell a phenotype distinguishable from that obtained in the absence of repair. (page 12, lines 14-22)

Thus, the specification provides for a genetic alteration (corepair of a marker). In order to initiate the corepair, the marker is present in a vector that has an initiating mismatch. The initiating mismatch activates methyl-directed mismatch repair system in a cell; and causes corepair of genetic elements present in the vector.

Claims 27-47 have been rejected under the judicially created doctrine of obviousness type double patenting over claims 1-12 of U.S. Patent no. 6,406,847. Without conceding to the correctness of the rejection, in order to further prosecution An executed terminal disclaimer is attached herewith.

Claims 24-47 have been rejected under 35 U.S.C. 112, first paragraph. The Office Action states that the specification, while being enabling for markers with mismatches of at least 5 nucleotides where the second mismatch is four nucleotides or less, does not reasonably provide enablement for markers of four of less mismatched nucleotides where the second mismatch is four nucleotides or less.

Applicants respectfully submit that the presently claimed invention meets the requirements of 35 U.S.C. 112, first paragraph. One of skill in the art could readily practice the claimed invention without undue experimentation.

The literature demonstrates that *in vitro* extracts from E. coli are capable of initiating repair with mismatches of greater than 4 nucleotides. In an analysis of mismatches capable of activating a methyl-directed mismatch repair system, Fang et al. (1997) J. Biol. Chem. 272:22714-221720, demonstrates that small mismatches of greater than 4 nucleotides will initiate repair. For example, the data provided in Table 3 and in Figure 3 (inserted below) depict graphically the level of repair that is initiated.

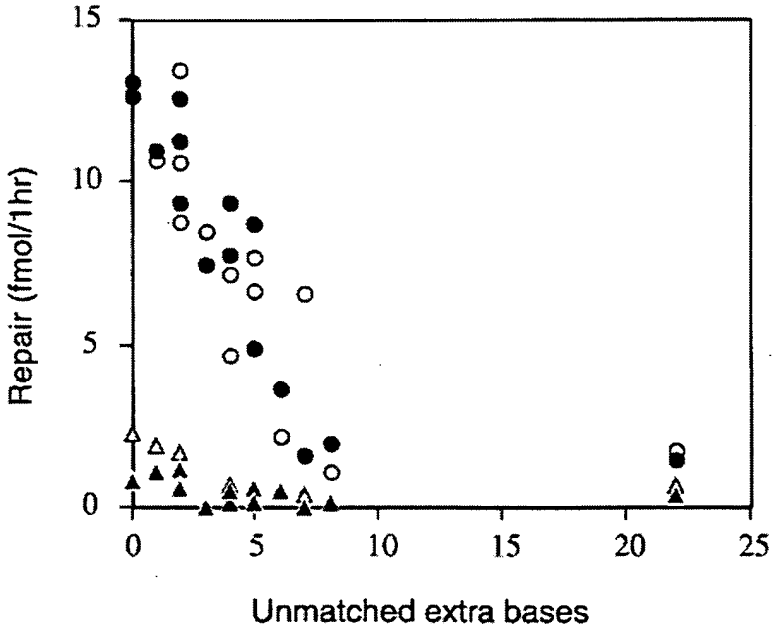

Figure 3. Dependence of methyl-directed small heterologies on the loop size and *mutS* gene product. Data are from Table III. *Symbols* at point 0 of unmatched extra bases represent base-base mismatches. *Circles*, wild-type extract reactions; *triangles*, *mutS* extract reactions. *Open symbols*, heteroduplexes with insertion on unmethylated viral strand (V-substrates); *closed symbols*, heteroduplexes with deletion on unmethylated viral strand (C-substrates).

As is demonstrated by these *in vitro* assays, there is no physical bar to the initiation of co-repair by mismatches greater then 4 nucleotides. The use of *in vivo* systems to initiate repair

with similar mismatches requires no more than routine experimentation by one of skill in the art. A Declaration under 37 C.F.R. 1.132 by Dr. Stephen del Cardayre accompanies this response and addresses these points.

As discussed by Dr. del Cardayre, it is reasonably expected that one of skill in the art could readily utilize a microbe to practice the presently claimed invention without undue experimentation. In view of the above amendments, remarks and accompanying exhibits and Declaration, Applicants respectfully submit that the present claims are patentable under 35 U.S.C. 112. Withdrawal of the rejection is requested.

Applicants submit that all of the claims are in condition for allowance, which action is requested. The Commissioner is hereby authorized to charge any other fees under 37 C.F.R. §§ 1.16 and 1.17 which may be required by this paper, or to credit any overpayment, to Deposit Account No. 50-0815, order number UCSF-127CIP2.

Respectfully submitted,

Date: March 29, 2005

By: Pamela J. Sherwood
Pamela J. Sherwood, Ph.D.
Registration No. 36,677

BOZICEVIC, FIELD & FRANCIS LLP
1900 University Avenue, Suite 200
East Palo Alto, CA 94303
Telephone: (650) 327-3400
Facsimile: (650) 327-3231